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Intervet/Schering-Plough Animal Health
PATENT DEPARTMENT
PO BOX 318
29160 Intervet Lane
MILLSBORO, DE 19966-0318

EXAMINER	
FORD, VANESSA L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,709	VERMEIJ, PAUL	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-13 and 15-19* is/are pending in the application.

4a) Of the above claim(s) *6,13,15,16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-12 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, 1-5, 9-12 and 17 filed August 21, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-6, 9-13 and 15-16 have been amended. Claims 17-19 have been added. Claims 6, 13, 15-16 and 18-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 21, 2008.

Claims 1-5, 9-12 and 17 are under examination.

Specification

Sequence Requirements

2. This application contains sequence disclosures, see paragraph [0162], for example that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.21(a)(1) and (a) (2). The amino acid sequence set forth at page 19 is not identified by a sequence identifier, e.g. SEQ ID NO. However, this application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 for the reasons(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action should include both compliance with the sequences and a response to the Office action set forth below. Failure to fully comply with ***both*** these requirements in the time period set forth in this Office action will be held non-responsive.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example, pages 3, 5 and 7. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Applicant is asked to review the entire specification for this type of informality and correction is required.

4. The use of the trademark has been noted in this application. See for example, page 12, Diluvac®Forte. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicant should review the specification for these kinds of informalities and correction is required.

5. The disclosure is objected to because of the following informalities: lines 10 to the remainder of the page is blank. Appropriate correction is required.

Claim Objection

6. Claim 1 is objected to from depending from nonelected claim 6. Correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-5 and 17 are rejected under 35 U.S.C. 101 because they are directed to non-statutory subject matter. The claims are directed to a "nucleic acid molecule or recombinant carrier or host comprising the nucleic acid molecule". This rejection may be obviated, if the claims are amended to "… "isolated or purified…".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

8. Claims 1-5 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is directed to the Written Description Training Materials, Revision 1, March 25, 2008. See Example 6, in particular. (Original Written Description Guidelines published in the Federal Register at 64 FR 71427, December 21, 1999 and in the Official Gazette at 1231 O.G. 123, February 29, 2000).

Independent claim 1 is drawn to a nucleic acid encoding the 26 kD *Lawsonia intracellularis* protein of claims 6 or a part of said nucleic acid that encodes an immunogenic fragment of said protein.

The specification discloses only one nucleic acid encoding a 26 kD protein, SEQ ID NO:1. The specification does not describe other species in the genus by structure or physical and/or chemical characteristics. The functions of the other species are not disclosed and there is no known or disclosed correlation between the unknown structure and the unknown function or between the unknown structures and the structure of the single species disclosed.

The specification proposes to discover other members of the genus by using a hybridization procedure. There is no description of the mutational sites that exist in nature and there is no description of how the structure of SEQ ID NO:1 relates to the

structure of different alleles. The general knowledge of the art concerning alleles does not provide any indication of how the structure of one allele is representative of other unknown alleles having concordant or discordant functions. The common attributes of individual alleles, other SEQ ID No.1 are not described. The nature of alleles is that they are variant structures where the structure and function of one does not provide guidance to the structure and function of others. In other words, the existence of other alleles is unpredictable and the structure of other alleles, if they exist, is also unpredictable. In addition, according to the standard definition, the genus might include members that have widely divergent functional properties.

Fragments or variants of SEQ ID NO: 1 do not meet the requirements under 35 U.S.C. 112 first paragraph. The skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, regardless of the complexity or simplicity of the method of isolation or purification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating or purifying. The nucleic acid and/or protein itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an

invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d 1966.

The following references provide evidence that the modifications in the nucleic acid sequence directly effects the gene product expressed.

Kleppe et al *(Tidsskr Nor Laegeforen, September 30, 2001; 121(23):2717-20)* teach that the main function of DNA is to code for protein, it is logical to examine the impact of mutations on protein structure and function (see the Abstract).Hoppner *(Horm Re. 2002, 58 Suppl. 3:7-15)* teaches that genetic aberrations, like chromosomes aneuploidy, gene translocations or mutations in key regulatory proteins often lead to clinical symptoms (see the Abstract). Hoppner teaches that minor genetic alterations like point mutations can affect the function of gene products (see the Abstract). Therefore base upon the teaching of the cited art, one of skill in the art could conclude that modifying a nucleic acid molecule has a direct affect on the protein and the function of the protein that is encoded by the nucleic acid molecule. In the instant case,

modifications along the DNA molecule could result in a protein encoded by the nucleic acid molecule that does not have the desired biological function.

One of skill in the art would conclude that the Applicant was not in possession of the claimed genus because the description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitutes a sufficient number of representative, the Courts have indicated what does not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

While the description of the ability of the claimed nucleic acid molecule which hybridizes may generically describe the nucleic acid molecule's function, it does not describe the nucleic acid molecule itself. The hybridization capability distinction is a purely functional distinction. Thus, those or skill in the art would not consider the

Applicant to be in possession of the claimed genus of nucleic acids based on a single species disclosed.

In view of all of the above, the specification fails to satisfy the written description requirement of 35 U.S.C. 112 first paragraph with respect to the full scope of the claims.

Scope of Enablement Regarding Fragments

9. Claims 1-5 and 9-12 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule comprising SEQ ID No.1, does not reasonably provide enablement for variants or fragments of SEQ ID NO. 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teach an embodiment of the invention that is directed nucleic acid molecules are a part of the nucleic acid molecule encoding the 26 KD Lawsonia intracellularis protein. These nucleic acid molecules encompass nucleic acid molecules having at least 90% homology(e.g. 92%, or 95% or 96 or even 98% homology) to SEQ ID NO.1 (page 3).

There is no guidance provided as to which amino acids can be deleted or substituted and still have the polynucleotide retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotide broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the nucleic acid sequence of the polynucleotide determines its structural and

functional properties, predictability of which changes can be tolerated in a polynucleotide's sequence and still retain similar activity requires a knowledge with regard to which nucleic acids in the polynucleotide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polynucleotide structure relates to function. However, the problem of the prediction of polynucleotide structure from mere sequence data and what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

Kleppe et al *(Tidsskr Nor Laegeforen, September 30, 2001; 121(23):2717-20)* teach that the main function of DNA is to code for protein, it is logical to examine the impact of mutations on protein structure and function (see the Abstract).Hoppner *(Horm Re. 2002, 58 Suppl. 3:7-15)* teaches that genetic aberrations, like chromosomes aneuploidy, gene translocations or mutations in key regulatory proteins often lead to clinical symptoms (see the Abstract). Hoppner teaches that minor genetic alterations like point mutations can affect the function of gene products (see the Abstract). Therefore base upon the teaching of the cited art, one of skill in the art could conclude that modifying a nucleic acid molecule has a direct affect on the protein and the function of the protein that is encoded by the nucleic acid molecule. In the instant case, modifications (e.g. multiple deletions) along the DNA molecule could result in a protein encoded by the nucleic acid molecule that does not have the desired biological function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple deletions of other types and the positions within the polynucleotide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple deletions. The sequence of some polynucleotides is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polynucleotides.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other polynucleotides having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polynucleotides that are variants or fragments of SEQ

ID NO:1 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the polynucleotide's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Enablement Regarding Host Cell

10. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 5 is drawn to a host cell comprising a nucleic acid according to claim 1.

Applicants broadly claim a transgenic cell containing a host cell transfected or transduced with a recombinant vector that directs expression of a nucleic acid molecule as recited in claim 1. These claims read on a cell within a transgenic animal given that the term "isolated" is not denoted in describing the transgenic cell. The breadth of the claim reads on the implementation of the transgenic cell in both *in vitro* and *in vivo* assays.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek *("Factors affecting transgenic animal production," Transgenic Animal Technology, 1994, pages 96-98)* taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Wall (*Theriogenology, 1996,Vol. 45, pp. 57-68)* teaches that the art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene. The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc., see Houdebine, *(J. Biotech. Vol. 34, 1994, pages 269-287, specifically page 281).* Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as

methylation or deletion from the genome, see Kappel, (*Current Opinions in Biotechnology, Vol. 3, 1992, pp. 548-553).*

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues. See Cameron, *(Molec. Biol. 7, 1997, pages 253-265, specifically page 256, col. 1 -2, bridg. parag.).* Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct. See Cameron, *(Molec. Biol. 7, 1997, page 256, lines 3-9).* With regard to the importance of promoter selection, Niemann, *(Transg. Res. 7, 1997, pages 73-75)*,states "that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health" (pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins, *(Hypertension, Vol. 22, 1993, pp. 630-633)* states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models for human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (*Nature, Vol. 344, 1990, 541-544)* produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer *(Cell, Vol. 63,*

1990, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. See Mullins *(EMBO J., vol. 8, 1989, pages 4065-4072; Taurog et al, Jour. Immunol., Vol. 141, 1988, pages 4020-4023).* Mullins *(J. Clin. Invest. Vol. 98, 1996. pages S37-S40)* disclose that the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Thus, at the time of filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species. Applicants can obviate the instant rejection by amending the claims to recite the term "isolated" before the recitation, "host cell".

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record

establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect predicting the phenotype of transgenics., 3) the reference cited above convey the state of the art regarding unpredictability of determining the phenotypes of trangenics, and 4) no working examples present in the specification regarding predicting the phenotypes of transgenic. 6) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art could not predict the phenotype of transgenics because of the lack of guidance in the art and in the instant specification in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Enablement Regarding Vaccine

11. Claims 1-5, 9-12 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Independent claim 1 is drawn to nucleic acid encoding the 26 kD *Lawsonia intracellularis* protein of claims 6 or a part of said nucleic acid that encodes an immunogenic fragment of said protein.

Dependent claim 9 is drawn to a vaccine for combating *Lawsonia intracellularis* infection comprising a nucleic acid according to claim 1 and a pharmaceutically acceptable carrier.

The specification has failed to teach or disclose a vaccine comprising transformed cells comprising a nucleic acid encoding the 26 kD *Lawsonia intracellularis* protein of claims 6 or a part of said nucleic acid that encodes an immunogenic fragment of said protein.

The specification teach expression of *L. intracellularis* gene 5608 from T7 promoter in *E. coli.* See pages 19-20. The specification teaches that samples were analyzed by western blot using pig and chicken serum. See pages 19-20. The specification teach that a reaction with protein 5608 was observed using the serum from the pig that had been orally challenged with purified *L. intracellularis* and with the chicken anti- *L. intracellularis serum.* See page 20.

The specification fails to enable the use of vaccines. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to *Lawsonia intracellularis* infection or disease induction. The specification contemplates that the vaccines of the can be used to combat *L. intracellularis.* See page 1. However, the specification has failed to administer the claimed nucleic acid molecule to a subject and perform challenge studies. The specification does not provide evidence that the

vaccines comprising the claimed nucleic acid molecules are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing *Lawsonia intracellularis* infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a DNA vaccine to induce protective immunity is problematic. Pal et al *(Vaccine 17, 459-65, 1999)* teach that direct injection of plasmid DNA in several systems containing the sequences of specific bacteria, viral and parasitic antigens has shown to result in expression of the foreign protein and induction of humoral and CMI responses and in some instances the DNA plasmids carrying sequences from antigens of different pathogens have been found to fail to induce a measurable immune response and/or protection against a challenge (page 463). Pal et al demonstrated that DNA plasmids encoding proteins (MOMP) elicited a modest immune response but did not protect against infection or disease (see the Abstract and pages 463-464). Babiuk et al *(Vaccine 17:1587-95, 1999)* teach that regulatory agencies are concerned about the potential of plasmids to integrate into host cells and to possibly precipitate aberrant cell division due to insertional mutation, chromosomal alterations or rearrangements, activation of oncogenes or inactivation of tumor-suppressive genes (page 1593). Babiuk et al teach that there is also concern about the possibility of inducing anti-DNA antibodies following DNA immunization (page 1593). Babiuk et al teach that DNA vaccines have a disadvantage in regard to being

used for veterinary purposes because the method of delivering the vaccine in livestock cannot occur in areas of the body containing hair (page 1594). Babiuk et al teach that this disadvantage may be overcome by administration of the vaccines to mucosal surfaces (page 1594). However, McNeela et al *(Advanced Drug Delivery Reviews, September 23, 2001, Vol. 51, No. 1-3, pp. 43-54*)(Abstract only) teach that naked DNA vaccines are often poorly immunogenic, especially when administered by mucosal routes (see the Abstract). The art indicates that it DNA immunization is very unpredictable. This vaccines may elicit an immune response but are often not protective. It would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy. One skilled in the art cannot make and use the claimed vaccines with the information disclosed in the specification. There is no disclosure in the instant specification regarding administering the claimed polynucleotide to a subject to protect against *Lawsonia intracellularis* infections and disease. It would require extended experimentation to make and use the vaccines commensurate with the claims.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance making and using vaccines comprising the claimed nucleic acid molecules, 3) the reference cited above convey the state of the art regarding unpredictability using DNA vaccines and 4) no working examples present in the specification regarding using the claimed vaccines to combat *Lawsonia intracellularis* infections. 6) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level).

Despite the knowledge in the art regarding DNA vaccines, the specification has not shown how to make and used the claimed vaccine. It is determined that there is limited guidance provided in the specification as to how to use the claimed invention and that it would require undue experimentation by the skilled artisan to use the invention commensurate with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1-5, 9-12 and 17 are rejected under 35 U.S.C. 102(e) as anticipated by Kapur et al *(WO 2004/033631 A1 filed October 1, 2003).*

Independent claim 1 is drawn to nucleic acid encoding the 26 kD *Lawsonia intracellularis* protein of claims 6 or a part of said nucleic acid that encodes an immunogenic fragment of said protein.

Kapur et al teach nucleic acid molecules unique to *Lawsonia intracellularis* (page 3). Kapur et al teach the inventions provides vectors as well as host cells comprising a nucleic acid of the invention (page 4). Kapur et al teach that elements necessary for expression include nucleic acid sequences that direct and regulate expression of nucleic acid coding sequences (page 16). Kapur et al teach that one example of an element necessary is a promoter sequence, for example, a *L. intracellularis*-specific promoter (e.g. from the same coding sequence being expressed or from a different coding sequence) or non-*L. intracellularis*-specific promoter (pages 16-17). Kapur et al teach that immunogenic compositions and vaccines comprising the nucleic acids of the invention (pages 29 and 32). Kapur et al teach a SEQ ID NO: 47 that is a nucleic acid molecule that is part of the claimed nucleic acid molecule SEQ ID NO.1. See the sequence alignment below.

```
  Query Match             63.4%;  Score 543;  DB 12;  Length 735;
  Best Local Similarity   100.0%;  Pred. No. 1.3e-131;
  Matches  543;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy        314 GAGTGGGAACATAGTGTGCCTGCTGAGAATTTTGGCAGAGCTTTTACTGAATGGCGCGAA
373
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GAGTGGGAACATAGTGTGCCTGCTGAGAATTTTGGCAGAGCTTTTACTGAATGGCGCGAA 60
```

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Qy        374 GGTCATCCTCTTTGTGTAGATAATAAAGGTAAAAGTTTCAAAGGACGAAAATGTGCAGAA
433
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GGTCATCCTCTTTGTGTAGATAATAAAGGTAAAAGTTTCAAAGGACGAAAATGTGCAGAA
120

Qy        434 AAAGTAAATAAAACATATAGATATATGCAGTCTGATATGTACAATTTGTTTCCAGCAGTC
493
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 AAAGTAAATAAAACATATAGATATATGCAGTCTGATATGTACAATTTGTTTCCAGCAGTC
180

Qy        494 GGGTCTGTCAATGCTGCGAGAAGCAATAAGCAATACTCAGAGTTACTTGGAGTTCAATCT
553
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 GGGTCTGTCAATGCTGCGAGAAGCAATAAGCAATACTCAGAGTTACTTGGAGTTCAATCT
240

Qy        554 GCTTTTGGAACGTGTGAGGCAAAAATAGATGGGAATAGATTCGAACCACCGGATAGAGCT
613
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 GCTTTTGGAACGTGTGAGGCAAAAATAGATGGGAATAGATTCGAACCACCGGATAGAGCT
300

Qy        614 AAAGGTCAAGTAGCCCGTGCTGCTCTTTATATGGATAAAGAGTACAAGGAATACAATCTA
673
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 AAAGGTCAAGTAGCCCGTGCTGCTCTTTATATGGATAAAGAGTACAAGGAATACAATCTA
360

Qy        674 AGTCGTCAGCAAAGAAGACTTTTTGAGGCTTGGAGTAATATGTATCCAGTCGATGAATGG
733
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 AGTCGTCAGCAAAGAAGACTTTTTGAGGCTTGGAGTAATATGTATCCAGTCGATGAATGG
420

Qy        734 GAGTGTACACGAGCCAAACGAATCGAATCTATACAGGGAAATGAAAATATTTTTGTAAAA
793
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 GAGTGTACACGAGCCAAACGAATCGAATCTATACAGGGAAATGAAAATATTTTTGTAAAA
480

Qy        794 AATATGTGTATCGAAAAGGGGTTATGGTAAACAAACGAGGACAATATAAATACTACCTAA
853
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 AATATGTGTATCGAAAAGGGGTTATGGTAAACAAACGAGGACAATATAAATACTACCTAA
540

Qy        854 GTA 856
                |||
Db        541 GTA 543
```

Kapur et al anticipate the claimed invention.

13. Claims 1-2 are rejected under 35 U.S.C. 102(b) as anticipated by EMBL-EBI Database, Accession No. BH795503 *(created October 24, 2002) online, http://.www.ebi.ac.uk/cgi-bin/embelfetch.*

Independent claim 1 is drawn to nucleic acid encoding the 26 kD *Lawsonia intracellularis* protein of claims 6 or a part of said nucleic acid that encodes an immunogenic fragment of said protein.

EMBL-EBI Database discloses Accession No. BH795503 which is a part of the nucleic acid molecule encoding the 26 KD *Lawsonia intracellularis* protein. The nucleic acid sequence set forth as Accession No. BH795503 anticipates the claimed invention.

Status of Claims

14. No claims allowed.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
November 21, 2008